REMARKS/ARGUMENTS

I. Status of Claims and Formal Matters

Claims 1-20 are pending in this application. Claims 14 and 15 have been withdrawn from consideration. Claims 1, 3 and 4 are proposed to be amended. Claims 9 and 11 are herein canceled. Upon entry of the proposed amendments, claims 1-8, 10 and 12-20 are pending with claims 1-8, 10, 12-13 and 16-20 under active consideration. Applicant respectfully requests entry of the proposed amendments.

Claim 1 is amended to recite that the FSH, GnRH, LH and ML substances are each selected from a Markush group of compounds. Support for this amendment may be found in the specification as filed, at least at paragraphs [0042] (FSH), [0037] (GnRH), [0029] (LH) and [0038] (ML). Claim 1 is also amended to remove superfluous language. Claim 3 is amended to correct a typographical error. Claim 4 is amended to include language inadvertently deleted in a previous amendment. Accordingly, no new matter is added by the proposed amendments.

II. Patentability Arguments

A. Claim Rejections

1) The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack of Written Description Should Be Withdrawn

Claims 1-13 and 16-20 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, according to the Examiner, "[w]hile having written description of the particular GnRH antagonists of claim 9 and compounds identified in the specification and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims." Applicant respectfully traverses this rejection in view of the amendments proposed herein.

Applicant herein amends claim 1 to recite that the FSH, GnRH, LH and ML substances are each selected from a Markush group of compounds specifically disclosed in the specification and/or examples, and for which the Examiner has acknowledged sufficient written description.

Accordingly, Applicants respectfully request the withdrawal of the rejections of claims 1-13 and 16-20 under 35 U.S.C. § 112, first paragraph.

2) The Rejections Under 35 U.S.C. § 112, Second Paragraph, For Indefiniteness Should Be Withdrawn

Claims 1-13 and 16-20 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctively claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that

> Applicants claim a method of using substances by their activity. However, the activity is vague and indefinite one does not know what activities are encompassed by substances having follicle stimulating hormone activity, substances having luteinising hormone activity because Applicants have defined the activity by the name of specific hormones not by what they do.

Applicants respectfully traverse this rejection in view of the amendments proposed herein and the following arguments.

As in initial matter, Applicants respectfully submit that, to the extent the rejection is based on a lack of specific hormones recited in the claims, that the amendment herein of claim 1 obviates the rejection.

Moreover, Applicants respectfully point out to the Examiner that one of ordinary skill in the art would find the claims to be clear in view of limitations directed to the required effect of each substance. For example, claim 1 requires: (1) an FSH substance "in an amount effective to stimulate multiple follicular development"; (2) a GnRH antagonist in an amount effective "to prevent a premature LH-surge"; (3) an ML substance "in an amount effective to stimulate resumption of meiosis and luteinisation." Thus, Applicants respectfully submit that the claims as amended are not indefinite and therefore respectfully request the withdrawal of the rejections of claims 1-13 and 16-20 under 35 U.S.C. § 112, second paragraph.

Claim 4 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly incomplete for omitting essential elements (recombinant LH per kg of body weight). This claim language was inadvertently deleted and has been added back to claim 4 by amendment herein, in accordance with the Examiner's suggestion. Accordingly, Applicants respectfully request the withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, second paragraph.

3) The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-4, 6-13, 16-17 and 20 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grondahl et al. (US 6,585,982) (hereinafter "Grondahl") in view of Matthieu et al. (US 2003/0092628) (hereinafter "Matthieu") and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst. Gynaec. JPN, 1995, Vol. 47, No. 11, pp. 1223-1229 (hereinafter "Ikenaga") and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419 (hereinafter "Bergh"). Applicants respectfully traverse this rejection.

According to the Examiner, Grondahl teaches a COH regimen comprising the administration of a GnRH agonist to suppress FSH and LH, follicle stimulation with FSH or human menopausal gonadotropin (hMG) (a mixture of FSH and LH derived from the urine of post-menopausal women), and induction of an LH surge using hCG, but fails to teach administration of a GnRH antagonist (or recombinant LH). The Examiner cites Matthieu as teaching the use of GnRH antagonists (ganirelix) to prevent premature LH surges and cites Ikenaga as teaching that a 3:1 ratio of FSH/LH achieved a higher rate of pregnancy, *inter alia*, than a 1:1 ratio of FSH/LH or FSH alone, in a GnRH agonist COH protocol. According to the Examiner, it would have been obvious to one of ordinary skill in the art to add the GnRH antagonist step of Matthieu to the method of Grondal and to make FSH:LH in a 3:1 ratio in the combined method of Grondal and Matthieu to achieve, *inter alia*, increased pregnancy rates

It is well settled law that teaching away of prior art is a strong indication of nonobviousness. See e.g. *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from that which applicant took. *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). As is discussed in detail below, Applicants respectfully submit that the Examiner has failed to provide a rationale for why one of ordinary skill in the art would have had a reason to combine the cited references. For at least this reason, Applicants submit that no *prima facie* case of obviousness has been established.

The disclosures of Grondahl and Ikenaga are in the context of GnRH *agonist* protocols. In the case of GnRH *antagonist* protocols, a more analogous prior art, at least one study indicates

that, in GnRH-antagonist treated primates, LH is not required for folliculogenesis and in fact observed higher fertilization rates following follicular stimulation with FSH alone than in the presence of LH with FSH. *See* Zelinksi-Wooten et al., 10(7):1658-66 (1995) (abstract), submitted herewith as Exhibit A (suggesting that "the presence of LH with FSH (1:1) during the pre-ovulatory interval impairs gametogenic events in the periovulatory period"). Thus, Zelinksi-Wooten teaches away from the presently claimed invention.

WO 01/00227 further teaches away from the invention as presently claimed. WO 01/0027 discloses that pregnancy rates observed following COH protocols using GnRH antagonists are lower than the pregnancy rates observed following COH protocols using GnRH agonists. This results from an inhibitory effect of GnRH antagonists on implantation/pregnancy when administered at the concentration necessary to suppress premature LH surges. WO 01/00227 teaches that no relationship exists between the implantation rate and level of LH. Thus, one of ordinary skill in the art at the time the present application was filed lacked any motivation for co-administering an LH substance during a GnRH antagonist regimen.

Moreover, even were one of ordinary skill in the art to look to the less pertinent GnRH agonist protocols, the majority of studies investigating the benefit of FSH-only preparations (versus FSH preparations including LH) in follicle stimulating regimens found that inclusion of LH during COS either provides no additional benefit over FSH alone or significantly reduces clinical pregnancy rates.[1] Importantly, these studies were meta-analysis studies (*see, e.g.* Daya *et al.*) and/or utilized very large sample sizes (*see, e.g.* Out *et al.*, "a prospective, randomized, assessor-blind study [in which] 18 centres from 11 European countries participated" encompassing 1000 cycles) and thus provide the most statistically relevant conclusions on this topic.

[1] *See, e.g.,* Daya *et al.*, Fertil. Steril., 64(2):347-354 (1995) (abstract; Exhibit B), concluding that "the use of FSH is associated with a **significantly higher** clinical pregnancy rate than hMG" (emphasis added); Out *et al.*, Hum. Reprod., 2(2):162-171 (1996) (Exhibit C), finding that "more oocytes were retrieved, more high quality embryos obtained and…a higher ongoing pregnancy rate [was seen]" in regimens using recombinant FSH (rFSH) alone than in regimens using urinary FSH or HMG and indicating that "rFSH has higher bioactivity than urinary FSH or HMG"; Crain *et al.*, Am. J. Obstet. Gynecol., 179(2):299-307 (1998) (abstract; Exhibit D), finding no discernible differences in hormonal response, oocyte recovery or embryonic growth among 1st, 2nd and 3rd generation urinary human menopausal gonadotropin preparations (each generation increasingly purified for FSH); and Argrawal *et al.*, Fertil. Steril., 73(2):338-43 (2000) (abstract; Exhibit E), finding no differences in clinical pregnancy rates between FSH and hMG in GnRH agonist protocols and finding that FSH alone was more efficacious in protocols where no pituitary desensitization was used.

In view of the foregoing, Applicants respectfully submit that the cited references, alone or in combination, fail to establish a *prima facie* case of obviousness. At the very least, one of ordinary skill in the art would have been led in a direction divergent from that taken by Applicants in view of the prior art, which in totality, teaches away from the presently claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of claims 1-4, 6-13, 16-17 and 20 under 35 U.S.C. § 103(a).

CONCLUSION.

Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below.

Respectfully submitted,
HOWREY LLP

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By: /David W. Clough/Reg. No. 36,107
David W. Clough, Ph.D.
Registration No.: 36,107
Direct Dial No.: (312) 595-1408

CUSTOMER NO.: 22930
HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
Telephone No.: (703) 663-3600
Facsimile No.: (703) 336-6950